In-hospital outcomes of catheter-directed thrombolysis in patients with pulmonary embolism

Hobohm, Lukas ; Schmidt, Frank P ; Gori, Tommaso ; Schmidtmann, Irene ; Barco, Stefano ; Münzel, Thomas ; Lankeit, Mareike ; Konstantinides, Stavros V ; Keller, Karsten

Abstract: AIMS Catheter-directed treatment of acute pulmonary embolism (PE) is technically advancing. Recent guidelines acknowledge this treatment option for patients with overt or imminent haemodynamic decompensation, particularly when systemic thrombolysis is contraindicated. We investigated patients with PE who underwent catheter-directed thrombolysis (CDT) in the German nationwide inpatient cohort. METHODS AND RESULTS Data from hospitalizations with PE (International Classification of Disease code I26) between 2005 and 2016 were collected by the Federal Office of Statistics in Germany. Patients with PE who underwent CDT (OPS 8-838.60 or OPS code 8-83b.j) were compared with patients receiving systemic thrombolysis (OPS code 8-020.8), and those without thrombolytic or other reperfusion treatment. The analysis was not prespecified; therefore, our findings can only be considered to be hypothesis generating. We analysed data from 978 094 hospitalized patients with PE. Of these, 41 903 (4.3%) patients received thrombolytic treatment [systemic thrombolysis in 4.2%, CDT in 0.1% (1175 patients)]. Among patients with shock, CDT was associated with lower in-hospital mortality compared to systemic thrombolysis [odds ratios (OR) 0.30 (95% 0.14-0.67); P = 0.003]. Intracranial bleeding occurred in 14 (1.2%) patients who received CDT. Among haemodynamically stable patients with right ventricular dysfunction (intermediate-risk PE), CDT also was associated with a lower risk of in-hospital mortality compared to systemic thrombolysis OR 0.55 [95% confidence interval (CI) 0.40-0.75]; P < 0.001 or no thrombolytic treatment [0.45 (95% CI 0.33-0.62); P < 0.001]. CONCLUSION In the German nationwide inpatient cohort, based on administrative data, CDT was associated with lower in-hospital mortality rates compared to systemic thrombolysis, but the overall rate of intracranial bleeding in patients who received CDT was not negligible. Prospective controlled data are urgently needed to determine the true value of this treatment option in acute PE.

DOI: https://doi.org/10.1093/ehjacc/zuaa026

thrombolysis in patients with pulmonary embolism. European Heart Journal: Acute Cardiovascular Care, 10(3):258-264.
DOI: https://doi.org/10.1093/ehjacc/zuaa026

ESC European Society of Cardiology

European Heart Journal: Acute Cardiovascular Care (2021) **10**, 258–264
doi:10.1093/ehjacc/zuaa026

ORIGINAL SCIENTIFIC PAPER

In-hospital outcomes of catheter-directed thrombolysis in patients with pulmonary embolism

Lukas Hobohm[1,2]*, Frank P. Schmidt[3], Tommaso Gori[2], Irene Schmidtmann[4], Stefano Barco[1,5], Thomas Münzel[2], Mareike Lankeit[1,6], Stavros V. Konstantinides[1,7†], and Karsten Keller[1,2,8†]

[1]Center for Thrombosis and Hemostasis (CTH), University Medical Center Mainz (Johannes Gutenberg University Mainz), Langenbeckstrasse 1, 55131 Mainz, Germany; [2]Department of Cardiology, University Medical Center Mainz (Johannes Gutenberg University Mainz), DZHK Standort Rhein-Main, Langenbeckstrasse 1, 55131 Mainz, Germany; [3]Department of Cardiology, Mutterhaus Trier, Feldstraße 16, 54290 Trier, Germany; [4]Institute for Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center Johannes Gutenberg University Mainz, Obere Zahlbacherstraße 69, 55131 Mainz, Germany; [5]Clinic of Angiology, University Hospital Zurich, Rämistraße 100, 8091 Zurich, Switzerland; [6]Department of Internal Medicine and Cardiology, Campus Virchow Klinikum (CVK), Charité – University Medicine, Augustenburgerplatz 1, 13353 Berlin, Germany; [7]Department of Cardiology, Democritus University of Thrace, Alexandroupolis, Greece; and [8]Medical Clinic VII, Department of Sports Medicine, University Hospital Heidelberg, Dragana, 68100 8: Im Neuenheimer Feld 410, 69120 Heidelberg, Germany

Received 14 July 2020; revised 16 September 2020; editorial decision 17 September 2020; accepted 21 September 2020; online publish-ahead-of-print 25 November 2020

Aims Catheter-directed treatment of acute pulmonary embolism (PE) is technically advancing. Recent guidelines acknowledge this treatment option for patients with overt or imminent haemodynamic decompensation, particularly when systemic thrombolysis is contraindicated. We investigated patients with PE who underwent catheter-directed thrombolysis (CDT) in the German nationwide inpatient cohort.

Methods and results Data from hospitalizations with PE (International Classification of Disease code I26) between 2005 and 2016 were collected by the Federal Office of Statistics in Germany. Patients with PE who underwent CDT (OPS 8-838.60 or OPS code 8-83b.j) were compared with patients receiving systemic thrombolysis (OPS code 8-020.8), and those without thrombolytic or other reperfusion treatment. The analysis was not prespecified; therefore, our findings can only be considered to be hypothesis generating. We analysed data from 978 094 hospitalized patients with PE. Of these, 41 903 (4.3%) patients received thrombolytic treatment [systemic thrombolysis in 4.2%, CDT in 0.1% (1175 patients)]. Among patients with shock, CDT was associated with lower in-hospital mortality compared to systemic thrombolysis [odds ratios (OR) 0.30 (95% 0.14–0.67); $P = 0.003$]. Intracranial bleeding occurred in 14 (1.2%) patients who received CDT. Among haemodynamically stable patients with right ventricular dysfunction (intermediate-risk PE), CDT also was associated with a lower risk of in-hospital mortality compared to systemic thrombolysis {OR 0.55 [95% confidence interval (CI) 0.40–0.75]; $P < 0.001$} or no thrombolytic treatment [0.45 (95% CI 0.33–0.62); $P < 0.001$].

Conclusion In the German nationwide inpatient cohort, based on administrative data, CDT was associated with lower in-hospital mortality rates compared to systemic thrombolysis, but the overall rate of intracranial bleeding in patients who received CDT was not negligible. Prospective controlled data are urgently needed to determine the true value of this treatment option in acute PE.

Keywords Catheter-directed thrombolysis • Systemic thrombolysis • Mortality • Pulmonary embolism

* Corresponding author. Tel: +49 6131 17 8380, Fax: +49 6131 17 8461, Email: lukas.hobohm@unimedizin-mainz.de
† These authors contributed equally and share last authorship.

Introduction

Pulmonary embolism (PE) represents an important cause of morbidity and mortality in the European population and around the world.[1,2] In patients with acute PE who present with haemodynamic instability, systemic (intravenous) thrombolysis is a potentially lifesaving treatment option by rapidly restoring pulmonary perfusion and reducing pulmonary vascular resistance.[3,4] However, systemic thrombolytic treatment also carries a substantial risk of major bleeding, including life-threatening intracranial haemorrhage.[5] These concerns may explain, at least in part, why only 20–30% of eligible patients with acute PE undergo systemic thrombolytic therapy.[6–8]

Catheter-directed thrombolysis (CDT) allows local slow infusion of a low dose of a thrombolytic agent directly into the pulmonary system. It can be performed with or without the use of ultrasound-emitting devices and has yielded promising results in the treatment of acute PE.[9–12] Current guidelines recommend considering percutaneous catheter-directed treatment for patients with high-risk PE, in whom (systemic) thrombolysis is contraindicated or has failed, or as rescue thrombolytic therapy for patients with haemodynamic deterioration on anticoagulation treatment.[3] However, the level of evidence supporting this recommendation is low, and the interventional options for PE treatment remain partly controversial due to the relatively small number of patients treated and the lack of adequately sized trials with clinical outcomes. Because of this, and in order to address the need for further evidence from the perspective of population research, we investigated the efficacy and safety outcomes of CDT compared to systemic thrombolysis and conservative treatment (management without thrombolysis or other reperfusion treatment) in the large German nationwide inpatient sample from 2005 to 2016.

Patients and methods

Data source and procedural code definitions

In the German Diagnosis Related Groups (DRG) system, diagnoses are coded according to the International Classification of Diseases and Related Health Problems, 10th Revision with German Modification (ICD-10-GM), and surgical, diagnostic, and interventional procedures according to the German Procedure Classification [OPS, surgery and procedures codes (Operationen- und Prozedurenschlüssel)]. All DRG diagnoses of hospitalized patients in German hospitals are collected by the Federal Office of Statistics (Statistisches Bundesamt).

Hospitalized patients diagnosed with PE (ICD code I26) between the years 2005 and 2016 were included. Patients who underwent CDT, either without (OPS 8-838.60) or with ultrasound assistance (OPS code 8-83b.j), were identified and included together in the 'CDT' group; these patients were compared with patients who underwent systemic thrombolysis (OPS code 8-020.8), and with patients who received neither thrombolytics nor any other reperfusion treatment. Of note, patients who underwent (i) surgical embolectomy (OPS code 5-380.42) or (ii) percutaneous treatment (thrombus fragmentation, OPS code 8-838.7; or rotational thrombectomy, OPS code 8.838.d0) without thrombolytic drugs at any dosage were excluded from all analyses in the present study in order to avoid bias regarding patient selection in view of the small size of these groups. Patients who received both systemic thrombolysis and CDT were also excluded from analysis.

Haemodynamically unstable patients with PE were defined as those who necessitated cardiopulmonary resuscitation (CPR) (OPS code 8-77) and/or presented with shock (ICD code R57). The 2019 ESC guideline also include 'persistent arterial hypotension' as a criterion for the definition of haemodynamic instability; however, this parameter could not be captured in the German nationwide inpatient sample. For further analysis, haemodynamically unstable patients were classified into the following subgroups: (i) patients who necessitated CPR and (ii) patients who presented with shock but without the need for CPR or mechanical ventilation (OPS codes 8-70 and 8-71).

Study outcomes

The outcomes used for our analysis were all-cause in-hospital mortality and intracranial bleeding (ICD code I61).

Ethical aspects

Since this study did not involve direct access to data of individual patients by the investigators, approval by an ethics committee and informed consent were not required, in accordance with German law.

Statistical methods

Analyses were performed on our behalf by the Research Data Center (RDC) of the Federal Statistical Office and the Statistical Offices of the federal states in Wiesbaden, Germany (source: RDC of the Federal Office of Statistics and the Offices of Statistics of the states, DRG Statistics 2005–2016, own calculations). Aggregated statistical results were made available to us based on SPSS codes (SPSS® software, version 20.0, SPSS Inc., Chicago, IL, USA), which we had sent to the RDC to conduct these analyses. Continuous variables are presented as median and interquartile range (IQR); categorical variables are provided as absolute numbers and corresponding percentages. Comparison of patients with CDT vs. conservative treatment (no systemic thrombolysis and no CDT) as well as CDT vs. systemic thrombolysis was performed using the Mann–Whitney *U* test for continuous variables and the Fisher's exact or χ^2 test, as appropriate, for categorical variables. Univariate and multivariate logistic regression models were performed to investigate the impact of CDT on the in-hospital mortality in comparison to no thrombolysis and of CDT in comparison to systemic thrombolysis. Results are presented as odds ratios (OR) and corresponding 95% confidence intervals (CIs). We fitted multivariate logistic regression models including the following covariates chosen based on clinical relevance and no obvious collinearity: age, sex, cancer (ICD codes C00-C97), coronary artery disease (ICD code I25), heart failure (ICD code I50), chronic obstructive pulmonary disease (COPD, ICD code J44), essential arterial hypertension (ICD code I10), diabetes mellitus (ICD codes E10–E14), chronic renal insufficiency (chronic renal insufficiency stages 3–5 with glomerular filtration rate <60 mL/min/1.73 m^2: ICD codes N18.3, N18.83, N18.84, N18.4, N18.5), surgery during in-hospital stay (OPS code 5), tachycardia (ICD codes I47 and R000),

syncope (ICD code R55), and hypoxia (ICD code J96). The multivariate analyses were extended by adding the Charlson index. The Charlson index was developed as a weighted index to predict risk of death within 1 year of hospitalization and contains 19 specific comorbid conditions.[13] Major bleeding was defined as the presence of intracerebral bleeding (ICD code I61), intraspinal bleeding (G95.10), haemopericardium (ICD code I23.0), haemoperitoneum (ICD code K66.1), haemarthrosis (M25.0), and/or transfusion of blood constituents (OPS code 8-800).[14]

The software SPSS (SPSS® software, version 20.0, SPSS Inc.) was used for statistical analysis. *P*-values of <0.05 (two-sided) were considered to be statistically significant.

Results

Catheter-directed thrombolysis between 2005 and 2016

From 2005 to 2016, a total of 1175 patients with PE underwent CDT in Germany. The annual incidence rate of use of CDT in hospitalized patients with PE in Germany was 0.1 cases per 1000 patients per year. These patients had a median age of 68 years and were hospitalized over a median period of 10 days (*Table 1*). Of patients who underwent CDT, 52 (4.4%) presented with tachycardia, 44 (3.7%) with syncope, 865 (73.6%) with right ventricular (RV) dysfunction, and 155 (13.2%) were coded with shock.

In total, 255 patients (19.1% of the population treated with CDT) died during hospital stay. Transfusion of erythrocytes was necessary in 234 (19.9%) of the patients treated with CDT, and 14 (1.2%) patients suffered an intracranial bleeding event (*Table 1*).

In-hospital outcomes after catheter-directed thrombolysis compared to no thrombolytic treatment

We focused on haemodynamically stable patients with acute PE and RV dysfunction (corresponding to the definition of intermediate-risk PE in recent guidelines[3]), comparing the hospital outcome of patients who underwent CDT with that of patients who received the current 'treatment standard' for this risk category, i.e. anticoagulation alone without thrombolysis or any other reperfusion modality.[3] Patients with acute PE who underwent CDT were younger [68 (IQR 53–76) vs. 72 (60–80) years; $P < 0.001$] than patients who received no thrombolysis. Comorbidities such as active malignancy (7.7% vs. 20.5%; $P < 0.001$), COPD (5.7% vs. 10.5%; $P < 0.001$), or renal insufficiency (6.0% vs. 7.9%; $P = 0.016$) were more often present in patients without thrombolysis than in patients treated with CDT, whereas CDT-treated patients more frequently exhibited parameters suggesting early haemodynamic compromise such as tachycardia (4.4% vs. 2.6%; $P < 0.001$) or syncope (3.7% vs. 2.3%; $P < 0.001$).

In-hospital mortality rates and intracranial bleeding rates in haemodynamically stable patients with PE and RV dysfunction who were treated with CDT are presented, in comparison to those who received no thrombolysis and no other reperfusion treatment, in *Figure 1A*; patients with RV dysfunction who underwent systemic thrombolysis are also displayed on this panel for comparison. CDT was associated with a lower risk of in-hospital mortality compared to management of PE without thrombolytic treatment [0.45 (95% CI 0.33–0.62); $P < 0.001$]. In parallel, however, CDT also was associated with a 1.5% intracranial bleeding rate (*Figure 1A*), which was significantly higher compared to that of patients who received no thrombolytic treatment [0.5%; OR 2.52 (95% 1.30–4.89); $P = 0.006$].

In-hospital outcomes after catheter-directed thrombolysis compared to systemic thrombolysis

Of the 41 903 patients with acute PE who received any type of thrombolytic treatment, those who underwent CDT were slightly younger [68 (IQR 53–76) vs. 69 (57–77) years; $P < 0.001$] and had a longer stay in hospital [10 (6–16) vs. 9 (3–16) days; $P < 0.001$] than the patients who received systemic thrombolysis. The frequency of comorbidities in each group is shown in *Table 1*. Right ventricular dysfunction (73.6% vs. 78.6%; $P < 0.001$), and haemodynamic instability presenting as shock (13.2% vs. 20.7%; $P < 0.001$) or need for CPR (16.6% vs. 42.4%; $P < 0.001$), all were less frequent in patients who received CDT in comparison to systemic thrombolysis (*Table 1*). No significant differences were observed with regard to the need for transfusion of erythrocytes, gastrointestinal or intracranial bleeding events (*Table 1*).

The in-hospital all-cause mortality rate was high (44.2%) in the entire patient population treated with any thrombolytic approach (CDT or systemic thrombolysis). In-hospital mortality rates and intracranial bleeding rates associated with CDT vs. systemic thrombolysis are shown in *Figure 1A* for haemodynamically stable and in *Figure 1B and C* for haemodynamically unstable patients with shock or need for CPR, respectively. In both haemodynamically stable and unstable patients, the risk of in-hospital mortality was lower in patients treated with CDT compared to systemic thrombolysis (*Take home figure*). Among unstable patients, a lower risk of in-hospital mortality was observed in patients with acute PE and shock who were treated with CDT in comparison to systemic thrombolysis [OR 0.30 (95% CI 0.14–0.67); $P = 0.003$]; in patients who underwent CPR, treatment with CDT also was associated with a lower risk of in-hospital death independently from age, sex, and comorbidities (*Take home figure*).

In patients with shock, no intracranial bleeding events occurred in the group treated with CDT compared to 1.3% of patients treated with systemic thrombolysis; in patients who needed CPR, intracranial bleeding occurred with a similar frequency in both the CDT and the systemic thrombolysis group (*Figure 1B and C*). Regarding temporal trends, in-hospital mortality of haemodynamically unstable patients with PE decreased significantly from 61.1% in 2005 to 54.1% in 2016 [β -0.92 (95% CI -1.73 to -0.11), $P = 0.026$]. Similarly, the rate of major bleeding events declined from 50.0% in 2005 to 29.7% in 2016 [β -2.09 (95% CI -4.09 to -0.01), $P = 0.040$] (Supplementary material online, *Figure S1*).

Among haemodynamically stable patients with PE and RV dysfunction, fewer patients treated with CDT died in comparison to those who received systemic thrombolysis (7.4% vs. 13.8%), along with a similar rate of intracranial bleeding events (1.5% vs. 1.7%) (*Figure 1A*). Accordingly, CDT was associated with a lower risk of in-hospital mortality compared to a treatment with systemic thrombolysis [OR 0.55 (95% CI 0.40–0.75); $P < 0.001$] independently of age, sex, and comorbidities (*Take home figure*).

Table 1 Baseline characteristics and outcomes of 41 903 patients with pulmonary embolism who underwent catheter-directed or systemic thrombolysis (cumulative data of the years 2005–2016)

Parameters	All patients (*n* = 41 903)	CDT (*n* = 1175; 2.8%)	Systemic lysis (*n* = 40 728; 97.2%)	*P*-value
Age (years)	69 (57–77)	68 (53–76)	69 (57–77)	**<0.001**
Sex (female)	21 973 (52.4%)	602 (51.2%)	21 371 (52.5%)	0.407
Comorbidities				
Obesity	5754 (13.7%)	178 (15.1%)	5576 (13.7%)	0.155
Coronary artery disease	5329 (12.7%)	188 (16.0%)	5141 (12.6%)	**0.001**
Surgery during hospital stay	20 405 (48.7%)	587 (50.0%)	19 818 (48.7%)	0.391
Active malignancy	3709 (8.9%)	91 (7.7%)	3618 (8.9%)	0.194
Heart failure	12 191 (29.1%)	279 (23.7%)	11 912 (29.2%)	**<0.001**
Chronic obstructive pulmonary disease	3346 (8.0%)	67 (5.7%)	3279 (8.1%)	**0.003**
Thrombophilia	475 (1.1%)	17 (1.4%)	458 (1.1%)	0.325
Arterial hypertension	16 552 (39.5%)	504 (42.9%)	16 048 (39.4%)	**0.017**
Renal insufficiency	3190 (7.6%)	70 (6.0%)	3120 (7.7%)	**0.032**
Diabetes mellitus	8874 (21.4%)	211 (18.0%)	8663 (21.3%)	**0.006**
Clinical parameters and adverse events during hospitalization				
Hypoxia	21 197 (50.6%)	416 (35.4%)	20 781 (51.0%)	**<0.001**
Syncope	1231 (2.9%)	44 (3.7%)	1187 (2.9%)	0.092
RV dysfunction	32 880 (78.5%)	865 (73.6%)	32 015 (78.6%)	**<0.001**
Gastrointestinal bleeding	735 (1.8%)	15 (1.3%)	720 (1.8%)	0.261
Transfusion of erythrocytes	9026 (21.5%)	234 (19.9%)	8792 (21.6%)	0.184
Major bleeding	9558 (22.8%)	243 (20.7%)	9315 (22.9%)	0.079
Shock	8569 (20.4%)	155 (13.2%)	8414 (20.7%)	**<0.001**
Need for cardiopulmonary resuscitation	17 462 (41.7%)	195 (16.6%)	17 267 (42.4%)	**<0.001**
Outcomes				
In-hospital mortality	18 526 (44.2%)	225 (19.1%)	18 301 (44.9%)	**<0.001**
Intracranial bleeding	707 (1.7%)	14 (1.2%)	693 (1.7%)	0.210

CDT, catheter-directed thrombolysis; RV, right ventricular. P values of <0.05 (two-sided) were considered to be statistically significant and were presented in bold letters.

In-hospital outcomes after catheter-directed thrombolysis without ultrasound assistance compared to ultrasound-accelerated thrombolysis

From 2014 to 2016, ultrasound-accelerated CDT was performed in 192 patients with acute PE. In comparison to CDT without ultrasound-assistance (199 patients), patients treated with ultrasound-accelerated CDT tended to be younger [66 (IQR 50–78) vs. 69 (56–79) years; $P = 0.090$] and less frequently exhibited signs of PE-related haemodynamic compromise such as RV dysfunction or need for CPR (Supplementary material online, *Table S1*). In a multivariate regression model, ultrasound-accelerated CDT was not associated with a significantly lower risk of in-hospital mortality compared to other CDT modalities (Supplementary material online, *Figure S2*).

Major bleeding complications in patients treated with catheter-directed thrombolysis

Overall, major bleeding was more frequently documented in patients treated with CDT who underwent surgery during the hospital stay as well as in those with cancer, heart failure, or signs of haemodynamic compromise such as hypoxia, shock, or need for CPR (Supplementary material online, *Table S2*). For surgery [OR 5.48 (95% CI 3.79–7.80); $P < 0.001$], cancer [OR 2.31 (95% CI 1.42–3.73); $P = 0.001$], CPR [OR 3.10 (95% CI 2.22–4.49); $P < 0.001$], and shock [OR 2.64 (95% CI 1.80–3.61); $P < 0.001$], an independent association with major bleeding was confirmed by multivariate analysis.

Discussion

In patients with PE and haemodynamic instability, systemic thrombolysis may be a lifesaving option.[7,8,15] However, since this therapeutic modality is also associated with a significantly increased risk of intracranial or fatal haemorrhage,[5] CDT techniques (reviewed in[16]) have been developed. Trials with surrogate outcomes and a number of cohort studies and registries have yielded promising results in patients undergoing CDT.[9,11,12,17–19]

In the present study, the annual incidence rate of CDT in hospitalized patients with PE in Germany was 0.1 cases per 1000 patients per year, which is lower than that reported in the USA (1.1 cases per 1000 patients per year).[20] Also, compared to previous data, the in-hospital mortality rate of patients who underwent CDT in Germany appears higher than that reported in cohorts from the USA.[12,19,21]

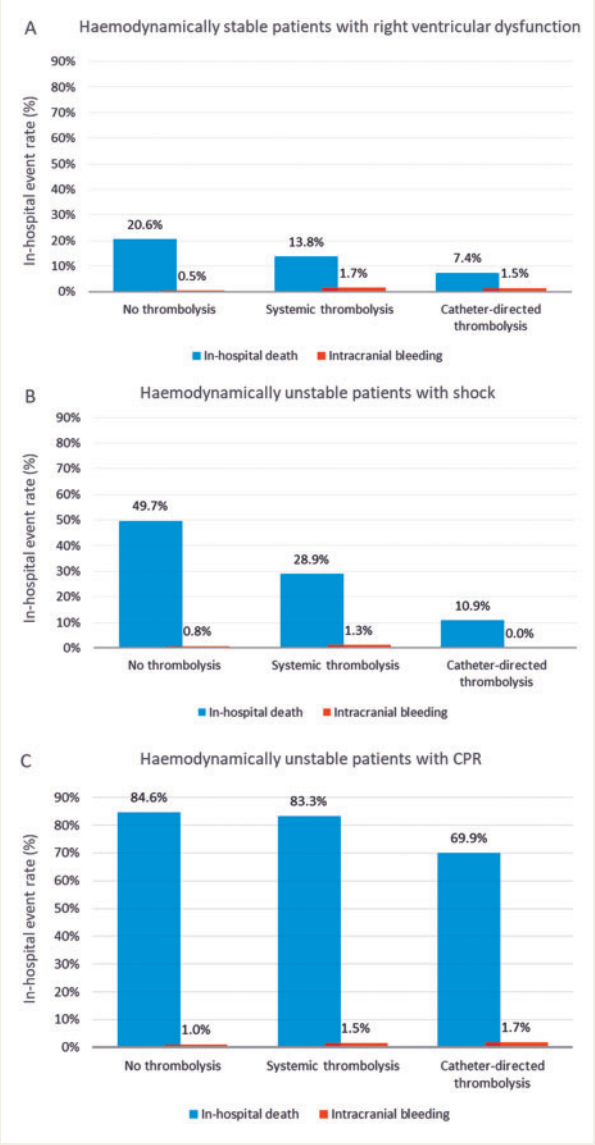


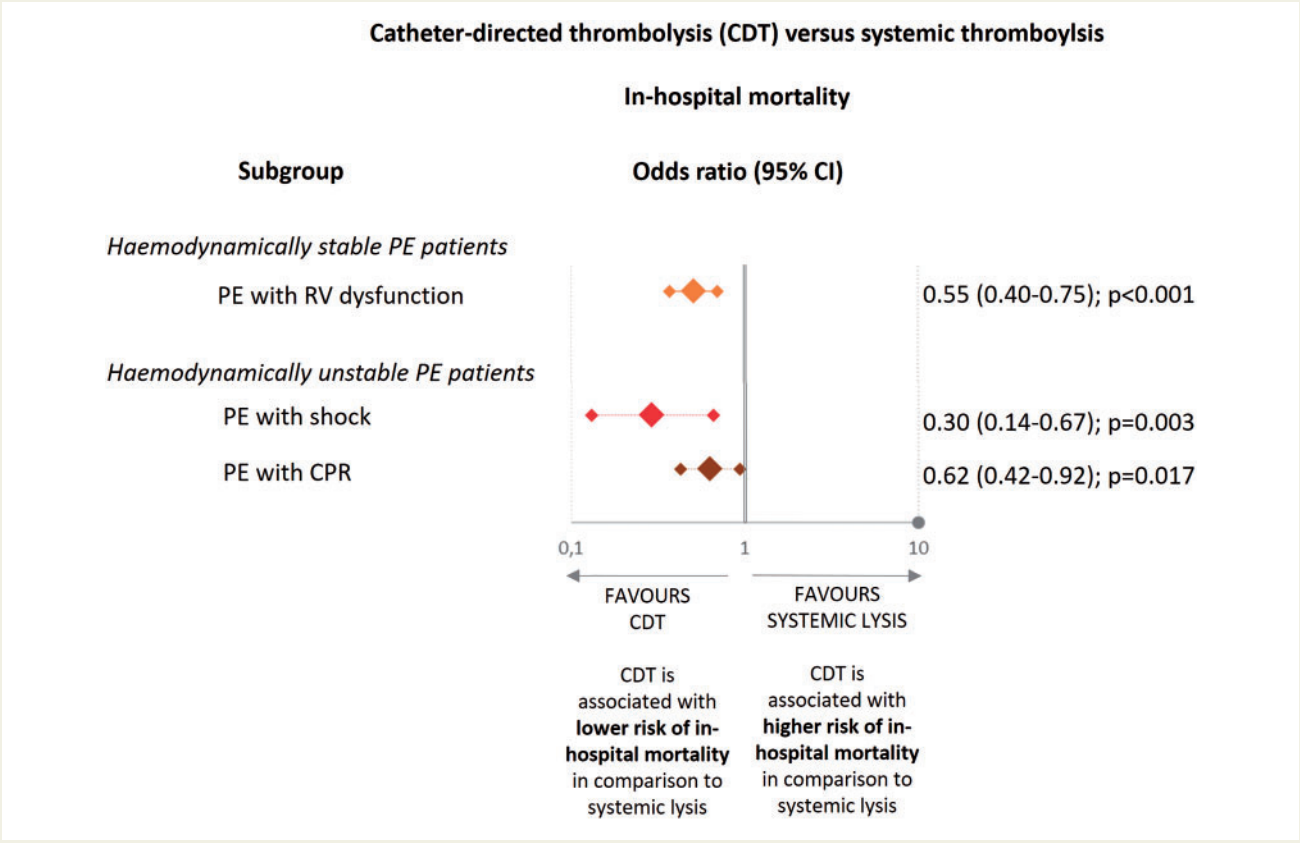
Figure 1 In-hospital mortality and intracranial bleeding rates in patients with pulmonary embolism and (*A*) right ventricular dysfunction, (*B*) shock, or (*C*) need for cardiopulmonary resuscitation, according to the route of administration of thrombolytic treatment. CPR, cardiopulmonary resuscitation.

However, the populations studied cannot be compared directly, as the German nationwide inpatient sample includes all documented interventions by both high-volume and low-volume centres in the country, and thus, by definition, no centre or patient selection bias exists. In this regard, it is worth mentioning that the CDT-treated patients in Germany were, on average, almost 10 years older than those reported from the USA, which might partly be responsible for their higher mortality rate.[20,22]

In view of existing data suggesting that CDT may be effective and acceptably safe in patients with PE, including those with haemodynamic instability,[12,21,23,24] current European guidelines suggest to consider CDT as an alternative reperfusion option for patients with high-risk PE, if they have a high bleeding risk and contraindications to systemic thrombolysis, or if systemic thrombolysis has been attempted and failed.[3] In the present analysis, CDT treatment of patients with shock was independently associated with a substantially (71%) lower risk of in-hospital mortality compared to systemic thrombolysis; in fact, no intracranial bleeding was reported during the hospital stay in patients with shock who were treated with CDT. However, it needs to be mentioned as a limitation of such comparisons within our study population that the available data did not include the exact dose of systemic thrombolytic treatment in each case.

Systemic thrombolysis is generally not recommended for haemodynamically stable patients with evidence of RV dysfunction (intermediate-risk PE),[3] because the risk of life-threatening bleeding complications appears to outweigh the clinical benefits.[25] In this context, CDT may have a potential role in intermediate-risk PE by relieving the right ventricle at a lower, 'acceptable' bleeding risk. In a randomized controlled trial of 59 haemodynamically stable patients with PE, parameters of RV function (a surrogate outcome) significantly improved after CDT compared with anticoagulation alone; no major bleeding complications occurred.[9] A prospective cohort study and a phase 2 randomized trial also yielded promising results on surrogate efficacy outcomes.[11,12] In contrast to the low mortality rate ranging between 0% and 1.7% in the above trials,[9,11,12] in the present nationwide inpatient sample, 7.4% of the haemodynamically stable patients with RV dysfunction treated with CDT died during hospitalization, which may again be related to the differences between the baseline characteristics of trial vs. 'real world' populations. However, our results also revealed that CDT was associated with a substantially lower risk (OR 0.45) of in-hospital mortality compared to management of PE without thrombolytic treatment. At the same time, CDT-treated 'stable' patients had a 1.5% intracranial bleeding rate in hospital, compared to a 0.5% rate among those treated with anticoagulation alone.

Our study has a number of limitations that must be kept in mind when interpreting the results. First, since our results are based on administrative data, we cannot exclude misclassification or inconsistencies. Additionally, this analysis of the German nationwide inpatient sample was not prespecified; therefore, our findings can only be considered to be hypothesis generating. Second, patients with acute PE, who are treated or died out of hospital or diagnosed post-mortem, are not included in the German nationwide inpatient sample. Third, we were able to study the association between variables registered during hospitalization, but had no information on their temporal or causal relationship. Fourth, the German nationwide inpatient sample does not report long-term outcomes after the discharge from hospital. Fifth, propensity score-based analyses were not performed, because the German Federal Statistical Office provides only aggregated data, minimizing the chances of controlling the process of case selection and matching. Finally, until 2014 no distinction was possible between ultrasound-accelerated and non-ultrasound-accelerated CDT. In the present study, patients undergoing ultrasound-accelerated CDT appeared to have lower death rates compared to patients treated with CDT without ultrasound assistance, but the differences could not be confirmed in the multivariate regression model; such comparisons must be considered explorative and serve for hypothesis generation.



Take home figure Association of route of administration of thrombolytic treatment with in-hospital mortality. Associations were presented as odds ratios and included the following parameters for adjustment: age, sex, cancer, coronary artery disease, heart failure, chronic obstructive pulmonary disease, arterial hypertension, renal insufficiency, diabetes mellitus, surgery during in-hospital stay, tachycardia, syncope, and hypoxia. CDT, catheter-directed thrombolysis; CI, confidence interval; CPR, cardiopulmonary resuscitation; PE, pulmonary embolism; RV, right ventricular.

In conclusion, our results obtained in the nationwide patient sample in Germany, revealed potentially relevant associations between CDT and outcomes in patients with acute PE. Significant differences, notably lower mortality rates, were observed both in comparison to systemic thrombolysis in haemodynamically unstable patients and in comparison to non-reperfusion treatment in haemodynamically stable patients with RV dysfunction. On the other hand, we observed a non-negligible rate of intracranial bleeding in patients who underwent CDT. Clearly, prospective controlled data from adequately powered trials with clinical outcomes are now urgently needed to determine the true value of CDT in acute PE.

Supplementary material

Supplementary material is available at *European Heart Journal - Acute Cardiovascular Care* online.

Acknowledgements

We thank the Federal Statistical Office of Germany (Statistisches Bundesamt, DEStatis) for providing the data and the kind permission to publish these results (Source: RDC of the Federal Statistical Office and the Statistical Offices of the Federal States, DRG Statistics 2005–2016, own calculations).

Funding

This study was supported by the German Federal Ministry of Education and Research (BMBF 01EO1503). The authors are responsible for the contents of this publication.

Conflict of interest: L.H. reports lecture/consultant fees from MSD and Actelion, outside the submitted work. T.G. reports having received consultancy and lecture honoraria from Abbott Vascular and Boston Scientific, outside the submitted work. S.B. received lecture/consultant fees from Bayer HealthCare, BTG Pharmaceuticals, and LeoPharma; and economical support for travel/congress costs from Daiichi Sankyo and Bayer HealthCare, outside the submitted work. M.L. reports having received consultancy and lecture honoraria from Actelion, Bayer, Daiichi Sankyo, MSD, Pfizer—Bristol-Myers Squibb and research funding from BRAHMS—Thermo Fisher scientific, all outside the submitted work. S.V.K. reports grants and personal fees from Bayer AG; research grants from Boehringer Ingelheim and Servier; research grants and personal fees from Actelion, Daiichi Sankyo, and Biocompatibles Group—Boston Scientific; personal fees from Pfizer—Bristol-Myers Squibb and MSD, all outside the submitted work. All other authors declared no conflict of interest.

References

1. Barco S, Mahmoudpour SH, Valerio L, Klok FA, Munzel T, Middeldorp S, Ageno W, Cohen AT, Hunt BJ, Konstantinides SV. Trends in mortality related to pulmonary embolism in the European Region, 2000-15: analysis of vital registration data from the WHO mortality database. *Lancet Respir Med* 2020;**8**:P277–P287.
2. Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. *Circ Res* 2016;**118**:1340–1347.
3. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing G-J, Harjola V-P, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Ní Áinle F, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL; ESC Scientific Document Group. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020;**41**:543–603.
4. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, Jenkins JS, Kline JA, Michaels AD, Thistlethwaite P, Vedantham S, White RJ, Zierler BK; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation* 2011;**123**:1788–1830.
5. Marti C, John G, Konstantinides S, Combescure C, Sanchez O, Lankeit M, Meyer G, Perrier A. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J* 2015;**36**:605–614.
6. Jimenez D, Bikdeli B, Barrios D, Quezada A, Del Toro J, Vidal G, Mahe I, Quere I, Loring M, Yusen RD, Monreal M; RIETE Investigators. Epidemiology, patterns of care and mortality for patients with hemodynamically unstable acute symptomatic pulmonary embolism. *Int J Cardiol* 2018;**269**:327–333.
7. Stein PD, Matta F. Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused. *Am J Med* 2012;**125**:465–470.
8. Keller K, Hobohm L, Ebner M, Kresoja KP, Munzel T, Konstantinides SV, Lankeit M. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. *Eur Heart J* 2020;**41**:522–529.
9. Kucher N, Boekstegers P, Muller OJ, Kupatt C, Beyer-Westendorf J, Heitzer T, Tebbe U, Horstkotte J, Muller R, Blessing E, Greif M, Lange P, Hoffmann RT, Werth S, Barmeyer A, Hartel D, Grunwald H, Empen K, Baumgartner I. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation* 2014;**129**:479–486.
10. Liang NL, Avgerinos ED, Marone LK, Singh MJ, Makaroun MS, Chaer RA. Comparative outcomes of ultrasound-assisted thrombolysis and standard catheter-directed thrombolysis in the treatment of acute pulmonary embolism. *Vasc Endovascular Surg* 2016;**50**:405–410.
11. Tapson VF, Sterling K, Jones N, Elder M, Tripathy U, Brower J, Maholic RL, Ross CB, Natarajan K, Fong P, Greenspon L, Tamaddon H, Piracha AR, Engelhardt T, Katopodis J, Marques V, Sharp ASP, Piazza G, Goldhaber SZ. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE trial. *JACC Cardiovasc Interv* 2018;**11**:1401–1410.
12. Piazza G, Hohlfelder B, Jaff MR, Ouriel K, Engelhardt TC, Sterling KM, Jones NJ, Gurley JC, Bhatheja R, Kennedy RJ, Goswami N, Natarajan K, Rundback J, Sadiq IR, Liu SK, Bhalla N, Raja ML, Weinstock BS, Cynamon J, Elmasri FF, Garcia MJ, Kumar M, Ayerdi J, Soukas P, Kuo W, Liu PY, Goldhaber SZ. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. *JACC Cardiovasc Interv* 2015;**8**:1382–1392.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987;**40**:373–383.
14. Schulman S, Kearon C; the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;**3**:692–694.
15. Kucher N, Goldhaber SZ. Management of massive pulmonary embolism. *Circulation* 2005;**112**:e28–e32.
16. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, Gibbs JS, Huisman MV, Humbert M, Kucher N, Lang I, Lankeit M, Lekakis J, Maack C, Mayer E, Meneveau N, Perrier A, Pruszczyk P, Rasmussen LH, Schindler TH, Svitil P, Vonk NA, Zamorano JL, Zompatori M. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Endorsed by the European Respiratory Society (ERS). *Eur Heart J* 2014;**35**:3033–3073.
17. Kaymaz C, Akbal OY, Hakgor A, Tokgoz HC, Karagoz A, Tanboga IH, Tanyeri S, Keskin B, Turkday S, Demir D, Dogan C, Bayram Z, Acar RD, Guvendi B, Ozdemir N, Tapson VF, Konstantinides S. A five-year, single-centre experience on ultrasound-assisted, catheter-directed thrombolysis in patients with pulmonary embolism at high risk and intermediate to high risk. *EuroIntervention* 2018;**14**:1136–1143.
18. Kaymaz C, Akbal OY, Tanboga IH, Hakgor A, Yilmaz F, Ozturk S, Poci N, Turkday S, Ozdemir N, Konstantinides S. Ultrasound-assisted catheter-directed thrombolysis in high-risk and intermediate-high-risk pulmonary embolism: a meta-analysis. *Curr Vasc Pharmacol* 2018;**16**:179–189.
19. Kuo WT, Banerjee A, Kim PS, DeMarco FJ Jr, Levy JR, Facchini FR, Unver K, Bertini MJ, Sista AK, Hall MJ, Rosenberg JK, De Gregorio MA. Pulmonary embolism response to fragmentation, embolectomy, and catheter thrombolysis (perfect): initial results from a prospective multicenter registry. *Chest* 2015;**148**:667–673.
20. Patel N, Patel NJ, Agnihotri K, Panaich SS, Thakkar B, Patel A, Savani C, Patel N, Arora S, Deshmukh A, Bhatt P, Alfonso C, Cohen M, Tafur A, Elder M, Mohamed T, Attaran R, Schreiber T, Grines C, Badheka AO. Utilization of catheter-directed thrombolysis in pulmonary embolism and outcome difference between systemic thrombolysis and catheter-directed thrombolysis. *Catheter Cardiovasc Interv* 2015;**86**:1219–1227.
21. Bloomer TL, El-Hayek GE, McDaniel MC, Sandvall BC, Liberman HA, Devireddy CM, Kumar G, Fong PP, Jaber WA. Safety of catheter-directed thrombolysis for massive and submassive pulmonary embolism: results of a multicenter registry and meta-analysis. *Catheter Cardiovasc Interv* 2017;**89**:754–760.
22. Liang NL, Avgerinos ED, Singh MJ, Makaroun MS, Chaer RA. Systemic thrombolysis increases hemorrhagic stroke risk without survival benefit compared with catheter-directed intervention for the treatment of acute pulmonary embolism. *J Vasc Surg Venous Lymphat Disord* 2017;**5**:171–176.e171.
23. Lin PH, Annambhotla S, Bechara CF, Athamneh H, Weakley SM, Kobayashi K, Kougias P. Comparison of percutaneous ultrasound-accelerated thrombolysis versus catheter-directed thrombolysis in patients with acute massive pulmonary embolism. *Vascular* 2009;**17**:S137–S147.
24. Avgerinos ED, Abou Ali AN, Liang NL, Rivera-Lebron B, Toma C, Maholic R, Makaroun MS, Chaer RA. Catheter-directed interventions compared with systemic thrombolysis achieve improved ventricular function recovery at a potentially lower complication rate for acute pulmonary embolism. *J Vasc Surg Venous Lymphat Disord* 2018;**6**:425–432.
25. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, Bluhmki E, Bouvaist H, Brenner B, Couturaud F, Dellas C, Empen K, Franca A, Galie N, Geibel A, Goldhaber SZ, Jimenez D, Kozak M, Kupatt C, Kucher N, Lang IM, Lankeit M, Meneveau N, Pacouret G, Palazzini M, Petris A, Pruszczyk P, Rugolotto M, Salvi A, Schellong S, Sebbane M, Sobkowicz B, Stefanovic BS, Thiele H, Torbicki A, Verschuren F, Konstantinides SV. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014;**370**:1402–1411.